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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,872	04/05/2001	Alan Solomon	044137-5029-US	3133

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,872	SOLOMON ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,32-34,37-45,50-52,57-61 and 63-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,32-34,37-45,50-52,57-61 and 63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20060518* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-2, 32-34, 37-45, 50-52, 57-61 and 63-68 are pending.

Applicants' amendment filed June 19, 2006 is acknowledged. Applicants' response has been fully considered. Claims 1, 37, 50, 58-59 and 64 have been amended, and claims 3, 46-49, 53-55 and 62 have been cancelled. Therefore, claims 1-2, 32-34, 37-45, 50-52, 57-61 and 63-68 are examined.

Withdrawn Claim Objections

2. The previous objection to claim 37 is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 8 of the amendment filed June 19, 2006.

Withdrawn Claim Rejections - 35 USC § 112

3. The previous rejection of claims 3, 46-49, 53-55 and 62 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicants' cancellation of the claims in the amendment filed June 19, 2006.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 32-34, 37-45, 50-52, 57-61 and 63-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of removing amyloid deposits from a subject comprising administering to the subject a specific amyloid fibrils such as synthetic fibrils composed of an immunoglobulin light chain polypeptide or whole

immunoglobulin light chain polypeptide homologous to the amyloid fibrils in the subject in an effective amount to generate an immune response, wherein the immune response promotes the removal of amyloid deposits from the subject; or a pharmaceutical composition formulated for removing amyloid deposits from a subject comprising a specific amyloid fibrils such as synthetic fibrils composed of an immunoglobulin light chain polypeptide or whole immunoglobulin light chain polypeptide, which are homologous to the amyloid fibrils in the subject; or the use of an anti-amyloid agent in the treatment of Alzheimer disease as indicated in the prior art, does not reasonably provide enablement for a method of removing amyloid deposits from a subject comprising administering to the subject amyloid fibrils in an effective amount to generate an immune response, wherein the immune response promotes the removal of amyloid deposits from the subject, and wherein the amyloid fibrils do not comprise amyloid β-protein; or a pharmaceutical composition formulated for removing amyloid deposits from a subject comprising amyloid fibrils, wherein the amyloid fibrils do not comprise amyloid β-protein; where the amyloid fibrils are heterologous to the amyloid fibrils in the subject, and the proteins in the amyloid fibrils are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1-2, 32-34, 37-45, 50-52, 57-61 and 63-68 are directed to a method of removing amyloid deposits from a subject comprising administering to the subject amyloid fibrils in an effective amount to generate an immune response, wherein the immune response promotes the removal of amyloid deposits from the subject; or a pharmaceutical composition formulated for removing amyloid deposits from a subject comprising amyloid fibrils, and wherein the amyloid

fibrils do not comprise amyloid β-protein. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the present invention provides a method of removing amyloid deposits from a patient, comprising administering amyloid fibrils to generate an immune response that will promote the removal of in vivo amyloid fibrils; and also provides a vaccine or pharmaceutical composition comprising an amyloid fibril and a carrier (page 10, paragraph [0035]). There are no indicia that the present application enables the full scope of the claims in view of the use of a vaccine or pharmaceutical composition comprising amyloid fibrils in the method of removing amyloid deposits from a subject as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding various amyloid fibrils contained in a pharmaceutical composition used in the method of removing amyloid deposits from a subject, which is not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification has demonstrated the use of a pharmaceutical composition containing a specific amyloid fibrils containing immunoglobulin light chain variable region in the method of removing amyloid fibrils in mice with AL-amyloidoma (paragraphs [0128]-[0131]), it has not demonstrated the pharmaceutical composition has removed amyloid fibrils in mice with AA-amyloidosis (immunoglobulin light chain heterologous to AA-amyloid fibrils) or other types of amyloidosis, or the use of a pharmaceutical composition containing various amyloid fibrils with different proteins in removing amyloid deposits in a subject.

(3). The state of the prior art and relative skill of those in the art:

The prior art indicates the use of a pharmaceutical composition comprising amyloid fibril components (e.g., amyloid-β peptide or its variants, homologous to amyloid fibrils of the patient) in the method of treating patients suffering from amyloidogenic disease to induce immune response against amyloid deposits in the patient (Schenk *et al.*, WO 99/27944), however, the art does not indicate the use of amyloid fibril components which are heterologous to amyloid fibrils of the patient in the treatment. Thus, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the use and the effect of a composition comprising various amyloid fibrils heterologous to amyloid fibrils of the patient in the treatment, to be considered enabling.

(4). Predictability or unpredictability of the art:

The claims encompass a method of removing amyloid deposits from a subject comprising administering to the subject amyloid fibrils to the amyloid fibrils in the subject in an effective amount to generate an immune response, or a pharmaceutical composition formulated for removing amyloid deposits from a subject comprising amyloid fibrils, wherein the amyloid

fibrils do not comprise amyloid β-protein. While the specification indicates the use of a pharmaceutical composition containing immunoglobulin light chain variable region in the method of removing amyloid fibrils in mice with AL-amyloidoma (paragraphs [0128]-[0131]), it has not demonstrated the pharmaceutical composition has removed amyloid fibrils in mice with AA-amyloidosis (immunoglobulin light chain heterologous to AA-amyloid fibrils) or other types of amyloidosis. The invention is unpredictable regarding the effects of the composition comprising various amyloid fibrils with different proteins in removing amyloid deposits in a subject.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of removing amyloid deposits from a subject comprising administering to the subject amyloid fibrils in an effective amount to generate an immune response; or a pharmaceutical composition formulated for removing amyloid deposits from a subject, wherein the amyloid fibrils do not comprise amyloid β-protein. While the specification indicates amyloid fibril encompasses fibrils of immunoglobulin light chain, amyloid A protein, beta 2-microglobulin, transthyretin, cystatin C variant, gelsolin, procalcitonin, PrP protein, amyloid beta-protein, ApoA, lysozyme, variants thereof or allelic variants thereof (paragraph 0078), and the use of a pharmaceutical composition containing immunoglobulin light chain variable region in the method of removing amyloid fibrils in mice with AL-amyloidoma (paragraphs [0128]-[0131]), it has not demonstrated the pharmaceutical composition has removed amyloid fibrils in mice with AA-amyloidosis (immunoglobulin light chain heterologous to AA-amyloid fibrils) or other type of amyloidosis. Furthermore, there are

no working examples demonstrating the effects of a composition containing various amyloid fibrils having different proteins in removing amyloid deposits. Since the specification fails to provide sufficient teaching on the use of a pharmaceutical composition comprising various amyloid fibrils heterologous to amyloid fibrils of the subject in the method of removing amyloid deposits, it requires undue experimentation to identify the amyloid fibrils that are active in removing amyloid deposits and to assess the effects of various amyloid fibrils in a subject.

(6). Nature of the Invention

The scope of the claims encompasses the use of a pharmaceutical composition comprising amyloid fibrils in removing amyloid deposits, but the specification has not demonstrated the effect of various amyloid fibrils heterologous to amyloid fibrils of the subject in the method of removing amyloid deposits. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants and associated methods, the outcome is unpredictable regarding the effects of various amyloid fibrils, and the teachings in the specification are limited, therefore, it requires undue experimentation to identify an active amyloid fibrils and to assess the effects of various amyloid fibrils in removing amyloid deposits from the subject.

Response to Arguments

Applicants indicate the specification fully enables the claims directed to a method of removing amyloid deposits from a subject comprising administering to the subject amyloid fibrils in an effective amount to generate an immune response, wherein the immune response promotes the removal of amyloid deposits from the subject, and wherein the amyloid fibrils do

not comprise amyloid β-protein in view of the Wands factors discussed. The specification provides the data supporting the removal of amyloid deposits from mice (see Example D, page 35 of the specification); and the attached reference of Schell et al. (Amyloid and Amyloidosis, pp.234-235, (2001)) provides evidence that amyloid fibrils heterologous to the amyloid fibrils in the amyloid deposits of a subject can remove the amyloid deposits from the subject. Furthermore, the claimed method of removing amyloid deposits from a subject can be accomplished with any amyloid fibrils because amyloid fibrils, irrespective of the precursor protein that they are made from, are structurally homologous molecules and thereby elicit a generic anti-fibril immune response, as discussed in the previous response, dated February 22, 2005. Therefore, the specification enables the claimed invention (pages 8-13 of the response).

The response has been considered, however, the argument is not fully persuasive because of the following reasons. While the specification demonstrates the use of a pharmaceutical composition containing specific amyloid fibrils (e.g., immunoglobulin light chain variable region) homologous to the amyloid deposits in AL-amyloidoma (paragraphs [0128]-[0131]), it does not show the use and effects of various amyloid fibrils having different proteins, either homologous or heterologous to the amyloid fibrils in amyloid deposits in the method of removing amyloid deposits from the subject. Although amyloid fibrils, irrespective of the precursor protein that they are made from, are structurally homologous molecules, and may be used to induce a cross-reactive immune response, the use/effect of amyloid fibrils, heterologous to the amyloid fibrils in amyloid deposits, in removing amyloid deposits from the subject is not known. Thus, it requires undue experimentation to identify active amyloid fibrils that effective in removing amyloid deposits among various amyloid fibrils containing many different proteins.

Regarding the reference of Schell et al. (2001) Amyloid and Amyloidosis, pp.234-235), it is a post-filing reference, which merely teaches the use of a specific amyloid fibrils (human λ light chain) heterologous to the amyloid fibrils in the amyloid deposits in removing the AA-related deposits from the subject. This post-filing reference does not provide teachings for enabling the full scope of the claims at the time of filing of the instant application. Therefore, the full scope of the claims is not enabled.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1, 2, 32-34, 37-45, 50-52, 57-61 and 63-68 are rejected under 35 U.S.C. 102(e) as being anticipated by Schenk (U.S. Patent 6,875,434), which claims the benefits of provisional application 60/080,970, filed April 7, 1998.

Schenk teaches a pharmaceutical composition comprising an active agent (e.g., a fibril peptide, aggregate form of Aβ, Aβ42 and Aβ1-40; column 8, lines 30-33) that is effective to induce an immune response against amyloid component (claim 59); and a method for treating a disorder characterized by amyloid deposition in a mammalian subject by administering a pharmaceutical composition comprising an active agent (e.g., a fibril peptide, aggregate form of Aβ, Aβ42 and Aβ1-40) that is effective to induce an immune response against amyloid component, and an excipient or adjuvant (column 3. line 58-column 5, line 9; claims 1, 39, 40, 64-68), where the anti-amyloid agents are derived from amyloid proteins which are known to be associated with certain forms of amyloid diseases and includes e.g., immunoglobulin light chain (AL), amyloid β protein precursor (Aβ) or fragments, mutants or proteolytic peptides thereof (column 15, line 43-column 16, line 30; column 18, lines 1-13; claims 2, 37, 38, 50-52, 58, 60-61); and such fragments, or analogs can be synthesized by solid phase peptide synthesis or recombinant expression, or obtained from natural sources (column 20, lines 3-29; claims 32-34, 57 and 63). Example I indicates PDAPP transgenic mice, which exhibit Alzheimer's-like pathology and are considered to be an animal model for Alzheimer's disease, are treated with aggregated Aβ42 (AN1792), most of treated mice had no detectable amyloid in their brains at 13 months of age in contrast to control mice, all of which showed significant brain amyloid burden (Figs. 2 and 7; column 16, line 3-64; claims 41-45). Since the claims recites the amyloid fibrils do not comprise amyloid β-protien, where the specification indicates amyloid β-protien has a

molecular weight of 4.2 Kda (paragraph [0015]), and Schenk teaches the use of a variant of amyloid β-protien such as aggregate form of Aβ42 and Aβ1-40 and other anti-amyloid agents, which meet the criteria of the claimed invention.

6. Claims 1, 32-34, 37-45, 57, 59 and 64-68 are rejected under 35 U.S.C. 102(a) as being anticipated by Schenk (WO 99/27944).

Schenk teaches a pharmaceutical composition comprising an active agent (e.g., aggregate form of Aβ, Aβ1–42 (AN1792) and Aβ1-40 (AN1528)) that is effective to induce an immune response against amyloid component (pages 4 and 5; claim 59); and a method for treating patients suffering from amyloidogenic disease such as Alzheimer's disease by administering amyloid-beta peptide (Aβ) or variants thereof to induce immune response against amyloid deposit in the patient, where the amyloid-beta peptide can be administered in aggregated form (e.g., Aβ1-42 or Aβ1–40) with an adjuvant, (page 3, lines 1-29; page 8, lines 20-24; page 13, lines 28-33; page 43, line 24-page 45, line 20; page 50; Fig. 7; claims 1, 37-40, 64-68), and the PDAPP transgenic mice treated with one Aβ peptide (e.g., Aβ 1-42) has 81% less total Aβ level at 15 months than the PBS-immunized group (Tables 2-4, page 43, line 24-page 45, line 20; claims 41-45). The Aβ peptide and its fragments, or analogs can be synthesized by solid phase peptide synthesis or recombinant expression, or obtained from natural sources (page 15, lines 24-27; claims 32-34, 57, 63). Since the claims recites the amyloid fibrils do not comprise amyloid β-protien, where the specification indicates amyloid β-protien has a molecular weight of 4.2 Kda (paragraph [0015]), and Schenk teaches the use of a variant of amyloid β-protien such as aggregate form of Aβ42 and Aβ1-40, which meet the criteria of the claimed invention.

Conclusion

7. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner

CHIH-MIN KAM
PRIMARY PATENT EXAMINER

CMK
August 24, 2006